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Investigation of dermatological manifestations in maintenance hemodialysis patients

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ABSTRACT

Aims: Skin findings are common in patients with both chronic kidney disease and undergoing hemodialysis. These findings are observed as nonspecific and specific dermatological manifestations. Our study aimed to describe the characteristics of dermatologic findings of patients with end-stage renal disease undergoing maintenance hemodialysis treatment and to investigate the relationship between these findings and the demographic and clinical features of those patients.

Methods: Patients who were admitted to a private hemodialysis clinic in August 2023 were prospectively analyzed. Age, gender, type of vascular access, hemodialysis duration, etiology of end-stage renal disease, duration and frequency of hemodialysis sessions, dermatological findings, and the most recent complete blood count, parathyroid hormone, calcium, phosphorus, urea, and creatinine levels were examined and the findings were documented. Calcium x phosphorus levels were calculated. Statistical significance was accepted as $p<0.05$.

Results: A total of 43 patients with chronic kidney disease undergoing maintenance hemodialysis were included in the study. 23 (53.5%) of the patients were female and 20 (46.5%) were male. The ages of the patients ranged from 28 to 86 years (mean age: 62.79±12.63). Xerosis was the most common dermatological finding with a rate of 90.7%. Hyperpigmentation was found in 46.5%, pruritus in 41.9%, nail disorders (subungual hyperkeratosis, absent lunula, koilonychia, half and half nail, onychorrhexis) in 37.2%, pallor in 30.2% and ecchymosis in 14%. In addition, 55.8% of the patients had mucosal changes (mucosal pallor, xerostomia, oral candidiasis, black hairy tongue, burning mouth), and 27.9% had hair findings (lusterless hair, sparse hair, telogen effluvium). Pruritus was more frequent in patients with higher predialysis urea levels (173.27±49.75 mg/dl vs. 137.04±38.19 mg/dl), ($p<0.011$). Xerosis and hair findings were more common in women (100% vs. 80%, 92% vs. 0%), ($p<0.039$, $p<0.001$). Hyperpigmentation was found more frequently in patients with long-term hemodialysis duration (median: 6.50 years vs. 2.00 years), ($p<0.003$).

Conclusion: Dermatologic findings are frequently observed in patients under maintenance hemodialysis treatment and may have a negative impact on quality of life. Therefore, dermatologic evaluation should be considered an essential part of treatment in patients under maintenance hemodialysis.

Keywords: Skin findings, chronic kidney disease, hemodialysis

INTRODUCTION

Chronic kidney disease (CKD) is seen in 8.5-9.8% of prevalence worldwide and is defined as structural kidney damage or functional impairment lasting longer than 3 months.[1] Especially in end-stage renal disease (ESRD), at least one dermatological finding can be observed in 50-100% of patients.[2] Moreover, these dermatological problems adversely affect the quality of life in those patients.[2-5] Dermatological findings related to CKD may be observed both during the progression of CKD and during hemodialysis (HD). The most common nonspecific dermatological findings include itching, dryness, hyperpigmentation, nail and hair disorders, mucosal changes, pallor, ecchymosis, and uremic frost, whereas specific dermatological conditions include acquired perforating diseases, calciphylaxis, calcinosis cutis, bullous disease and nephrogenic systemic fibrosis.[2,3,6] Since the dermatologic aspect of HD is a neglected topic, in this study, we aimed to contribute to the current literature by evaluating dermatological findings in patients with ESRD under maintenance hemodialysis and investigating the relationship between dermatologic manifestations and clinical and demographic characteristics of the patients.

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METHODS

The study was carried out with the permission of Medicana International Ankara Hospital Ethics Committee (Date: 14.07.2023, Decision No: 16). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This single-center prospective cross-sectional study was conducted at a private dialysis center in Ankara in August 2023. A total of 43 patients aged ≥18 years with ESRD undergoing maintenance hemodialysis were intended to participate in the study. Written informed consent forms were obtained from the patients. Demographic characteristics, including age, gender, primary etiology and duration of CKD, as well as the duration and frequency of HD, types of access for HD, and dermatological findings, were also recorded from the registries of the dialysis center. Patients with primary dermatological diseases, those under topical treatment, and individuals with cirrhosis were excluded. Xerosis and pruritus were classified as local if they were present on the extremities or in one region and generalized if they did not fit the criteria for local involvement. Pigmentation disorders were classified as palmoplantar, diffuse, mucosal, and photosensitive areas. Nail findings (absent lunula, half and half nail, koilonyhcia, onychorrexis, Mees lines, subungual hyperkeratosis), hair findings (lusterless hair, sparse hair, telogen effluvium), and mucosal findings (mucosal pallor, xerostomia, oral candidiasis, black hairy tongue, burning mouth, macroglossia, taste changes, gingival bleeding) were screened and when more than one finding was detected for each patient, all findings were recorded.

Statistical Analysis

SPSS Version 22.0 for Windows (Statistical Package for the Social Sciences) was used for analyses of data. The normality of the numeric variables was tested by using Kolmogorov-Smirnow and skewness and kurtosis tests. Parametric and nonparametric variables were presented as mean ± standard deviation and median (minimum and maximum), respectively. Categorical variables were presented as percentages. Independent Samples T-test was used in comparisons of parametric variables. Pearson's chi-squared test and Fisher's exact test were used for comparison of categorical variables. Statistical significance was accepted as $p<0.05$.

RESULTS

A total of 43 patients were evaluated. Of these patients, 23 (53.5%) were female, and 20 (46.5%) were male. The ages of the patients ranged from 28 to 86 years (mean age: 62.79±12.63). The median HD duration was 3 (0.5-15) years. Twenty-nine patients (67.4%) received HD treatment via a functioning arteriovenous fistula, while 14 patients (32.6%) had a central venous catheter. Thirty-three patients (76.7%) underwent HD sessions three times a week, and ten patients (23.3%) received treatment twice a week. The most common comorbidities in this cohort were hypertension (HT) and diabetes mellitus (DM). Demographic and clinical characteristics of the patients are provided in Table 1.

Table 1. Demographic and clinical characteristics of the patients

	n (%) (Total n=43)
Gender	
Female	23 (53.5)
Male	20 (46.5)
Age (year)	
Mean±Sd (min-max)	62.79±12.63 (28-86)
Hemodialysis duration (year)	
Median (min-max)	3 (0.5-15)
Hemodialysis frequency	
Two times/week	10 (23.3)
Three times/week	33 (76.7)
Hemodialysis access	
Central venous catheter	14 (32.6)
Arteriovenous fistula	29 (67.4)
Co-morbidities	
None	8 (18.6)
HT	14 (32.6)
DM	6 (14)
HT+DM	13 (30.1)
HT+Thyroid disease	2 (4.7)
Primary etiology of ESRD	
Unknown	4 (9.3)
HT	12 (27.9)
DM	6 (14)
HT+DM	8 (18.6)
HT+DM+CHF	2 (4.7)
DM+Hereditary hemorrhagic telangiectasia	1 (2.3)
Nephrotic syndrome	4 (9.3)
Polycystic kidney disease	2 (4.7)
Drug	3 (7)

HT:hypertension, DM:diabetes mellitus, CHF:chronic heart failure, ESRD: end stage renal disease

Laboratory findings were analyzed in terms of leukocyte, hemoglobin, platelet, calcium, phosphorus, Ca x P, parathyroid hormone, urea and creatinine levels at the time of admission and the mean levels were determined. Ca x P levels of the patients are mostly lower than 55 (86%, n=37) for this reason advanced statistical analysis was not performed (Table 2).

Table 2. Laboratory findings in the patients

	Mean±Sd
WBC (cell/mcL)	7457.07±2197.44
Hemoglobin (g/dl)	10.77±2.00
Platelets (cell/ml)	212000±72588
Calcium (mg/dl)	8.09±1.01
Phosphor (mg/dl)	5.20±1.46
CaxP (mg^2/dl^2)	41.89±21.26
Parathyroid hormone (pg/ml)	367.95±225.20
Urea (mg/dl)	152.57±46.63
Creatinine (mg/dl)	8.20±2.81

All patients had at least one skin or mucosa finding (100%, n=43). Xerosis was the most common finding with a rate of 90.7% (n=39). Hyperpigmentation was found in 46.5% (n=20), pruritus in 41.9% (n=18), nail disorders in 37.2% (n=16), pallor in 30.2% (n=13) and ecchymosis in 14% (n=6). In addition, 55.8% (n=24) of the patients had mucosal changes, 27.9% (n=12) had hair findings, and 20.9% (n=9) had nail or mucosal fungal infection. None of the patients had uremic frost, keratosis pilaris, or issues at the insertion site, and no ESRD-specific dermatosis was observed except calcinosis cutis (n=1).

Xerosis and pruritus were most commonly localized in the extremities. Hyperpigmentation was observed in photo-exposed areas (face, upper extremities). Ecchymosis was mostly observed in the forearms and dorsum of the hands. The most common nail findings were the absence of lunula and subungual hyperkeratosis (14%, n=6). Among the mucosal findings, mucosal pallor (32.6%, n=14) was predominant and lusterless hair was the most common hair finding (**Table 3**), (**Figure**).

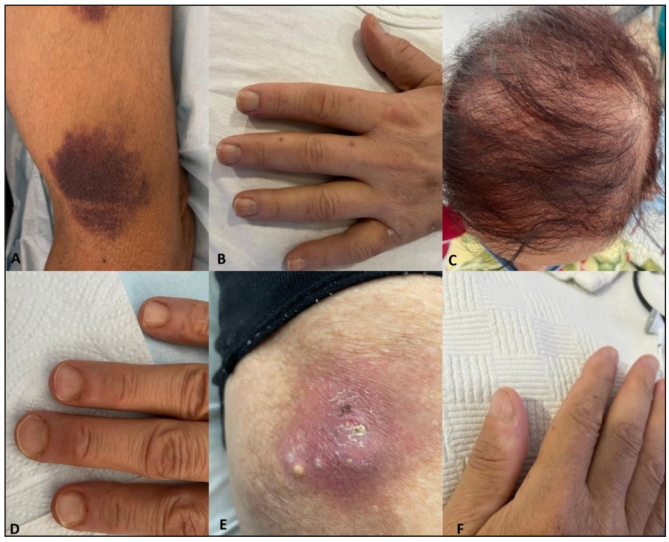

Figure. A: Ecchymosis, B: Half&half nail, C: Hair loss, D: Koilonychia, E: Calcinosis cutis, F: Absent lunula

Table 3. Dermatologic findings in the patients

	n (%) (total n=43)
Xerosis	
No	4 (9.3)
Yes	39 (90.7)
Localized	28 (65.1)
Generalized	11 (25.6)
Pruritus	
No	25 (58.1)
Yes	18 (41.9)
Localized	10 (23.3)
Generalized	8 (18.6)
Pallor	
No	30 (69.8)
Yes	13 (30.2)
Hyperpigmentation	
No	23 (53.5)
Yes	20 (46.5)
Ecchymosis	
No	37 (86)
Yes	6 (14)
Nail findings*	
No	27 (62.8)
Yes	16 (37.2)
Absent lunula	6 (14)
Subungual hyperkeratosis	6 (14)
Koilonychia	3 (7)
Half and half nail	2 (4.7)
Onychorrhexis	2 (4.7)
Mucosal findings*	
No	19 (44.2)
Yes	24 (55.8)
Pallor of mucosa	14 (32.6)
Xerostomia	10 (23.3)
Oral candidiasis	6 (14)
Black hairy tongue	6 (14)
Burning mouth	1 (2.3)
Hair findings*	
No	31 (72.1)
Yes	12 (27.9)
Lusterless hair	9 (20.9)
Telogen effluvium	4 (9.3)
Sparse hair	2 (4.7)
Calcinosis cutis	
No	42 (97.7)
Yes	1 (2.3)
Infections	
No	30 (69.8)
Yes	13 (30.2)

*Patients have more than one finding.

There was a statistically significant relationship between xerosis and hair findings and gender. Xerosis and hair findings were more common in women (100% vs. 80%, 92% vs. 0%), (p<0.039, p<0.001). The mean age in patients with nail finding-free (65.56±13.87 years) was higher compared to patients with nail findings (58.13±8.77 years, p<0.037). The patients with mucosal findings (mean age: 66.38±11.44 years) were older than patients with non-mucosal findings (mean age: 58.13±8.77 years, p<0.038).

Hyperpigmentation was found more frequently in patients with long-term hemodialysis and the difference was statistically significant (median: 6.50 years vs. 2.00 years, p<0.003).

The mean urea level was higher in patients with pruritus (173.27±49.75 mg/dl vs. 137.04±38.19 mg/dl), (p<0.011), whereas urea level was lower in patients with xerosis compared to patients without xerosis (147.47±44.82 mg/dl vs. 201.00±38.49 mg/dl), (p<0.027). Phosphorus, and creatinine levels were lower in patients with xerosis compared to those without xerosis (5.10±1.49 mg/dl vs. 6.24±0.74 mg/dl), (8.04±2.91 mg/dl vs. 9.72±0.74 mg/dl), (p<0.041, p<0.013, respectively). The mean hemoglobin level and the mean creatinine level were lower in patients with ecchymosis (9.61±0.65 g/dl vs. 10.95±2.06 g/dl), (5.96±1.88 mg/dl vs. 8.58±2.79 mg/dl), (p<0.005, p<0.034, respectively) (Table 4).

DISCUSSION

In the current study, skin and mucosal findings were evaluated in patients with ESRD patients undergoing HD and it was observed that all patients had at least one skin or mucosa finding. The most common finding was xerosis with 90.7%. Xerosis was most commonly localized and seen on the extremities, whereas in more severe cases, it was observed all over the body. In other studies, xerosis was reported with rates ranging from 54.8% to 96%.[7-12] In a meta-analysis of studies conducted in patients with ESRD in Iran, results ranging from 7.3 to 78.3% were reported.[13] Conducting the studies in different seasons and environmental factors may explain these differences. In other studies reported from Turkey, the prevalence of xerosis was found to be 87% and 98%, similar to our study.[14,15] It has been suggested that dryness is due to a defect in the structure of the stratum corneum or a functional abnormality in the eccrine sweat glands. However, it has been reported in other studies that there is no correlation between dry skin and water content of the stratum corneum[16] and changes in vitamin A metabolism, excessive diuretic use and chemical irritations are among the factors blamed for xerosis.[11,16] In our study, xerosis was found more frequently in women and urea, creatinine and phosphorus levels were lower in patients compared to those without xerosis.

Pruritus is another finding that affects the quality of life negatively. Pruritus was found with a rate of 41.9% in our study; localized and generalized pruritus rates were found to be close to each other. Pruritus is observed at a higher rate in patients on dialysis among patients.16 It has been reported to be observed more frequently in HD and to occur at a higher rate, especially as the duration of HD increases.[4] In other studies, rates ranging between 19.3-58.3% have been reported.[7-15] Inadequate dialysis, hyperparathyroidism, calcium and phosphorus dysregulation, xerosis, elevated magnesium and aluminum levels, anemia, male gender, hypervitaminosis-A, increased beta-2 microglobulin levels, HLA-B35, congestive heart failure and neurological disease, sensitivity to dialysis components, mast cell proliferation, and low vitamin D levels are among the factors accused in the etiology of pruritus.[2,9] In our study, pruritus was found more frequently in patients with high urea levels. However, no relation was found between parathyroid hormone, calcium, phosphorus levels and creatinine levels and

Table 4. The relationship between demographic and laboratory characteristics of patients and dermatological findings

p value	Xerosis	Pruritus	Pallor	Hyper pigmentation	Ecchymosis	Nail findings	Mucosal findings	Hair findings
Gender [a,b]	**0.039*[a]**	0.40	0.98	0.10	0.19	0.32	0.47	**<0.001***
Age [c]	0.27	0.96	0.62	0.25	0.076	**0.037***	**0.038***	0.090
HD duration [c]	0.49	0.68	0.063	**0.003***	0.88	0.85	0.24	0.10
HD frequency [b]	>0.99	0.48	0.14	0.73	0.61	>0.99	0.73	0.24
HD access [a,b]	0.29	0.57	0.077	0.32	0.077	0.89	0.90	0.72
Calcium [c]	0.10	0.38	0.71	0.50	0.56	0.51	0.49	0.84
Phosphor [c]	**0.041***	0.29	0.75	0.68	0.74	0.95	0.37	0.16
WBC [c]	0.23	0.94	0.50	0.42	0.24	0.12	0.65	0.41
Hemoglobin [c]	0.10	0.28	0.058	0.59	**0.005***	0.74	0.75	0.79
Platelets [c]	0.43	0.87	0.54	0.81	0.45	0.55	0.27	0.24
Parathyroid hormone [c]	0.66	0.090	0.72	0.14	0.11	0.61	0.72	0.20
Urea [c]	**0.027***	**0.011***	0.67	0.16	0.30	0.74	0.68	0.47
Creatinine [c]	**0.013***	0.37	0.87	0.20	**0.034***	0.10	0.13	0.75
Xerosis [a]		0.628						

*If p value<0.05 the result is indicated in bold, HD: hemodialysis, a: Chi-squared test, b: Fisher's exact test, c: Samples t-test

pruritus. No correlation was found between dryness and pruritus. Although studies are reporting that parathyroid hormone elevation causes pruritus, the lack of correlation between parathyroid hormone, calcium, phosphorus and uremic pruritus in other studies suggests that other factors may play a role in the etiology of uremic pruritus.[9,11,17]

Pallor was found with a rate of 30.2% in our study. In other studies, rates between 3.9-60% have been reported in HD patients.[7-10,14] Pallor is generally associated with anemia and accumulation of some fat-soluble pigments and hemosiderin in the skin.6 In our study, no significant correlation was found between hemoglobin level and pallor.

Hyperpigmentation was observed in 46.5% of the patients and was localized in photosensitive areas. In previous studies, the frequency of hyperpigmentation was found between 9.2-62%.[7-11,14] The diffuse hyperpigmentation observed in the photo-exposed areas is due to increased melanin in the basal layer and this is due to poor dialyzed of β-Melanocyte stimulating hormone (β-MSH). Increased pigmentation is observed more frequently as the duration of HD increases.[16] In our study, the increase in pigmentation with long-term HD and CKD was consistent with this literature.

Ecchymosis was localized especially on the forearms and was observed more frequently in patients with low hemoglobin and creatinine values among laboratory findings. It has been reported that increased skin fragility, heparin use and high urea levels may alter platelet aggregation.[11,18] In studies, rates ranging between 9% and 60% have been reported.[10,11,18]

When nail findings were analyzed in the current study, the most common findings were the absence of lunula and subungual hyperkeratosis. Patients with nail findings were younger, but no difference was found in laboratory tests. Many nail findings may occur due to both CKD and HD. The most common nail abnormalities are half-and-half nails and the absence of lunula. Although half and half nail has been reported most frequently in studies, the most frequently reported nail abnormality in studies conducted in our country has been the absence of lunula.[14,19] The absence of a lunula is one of the most common findings in our study and may be observed in conditions other than presence of CKD. It has been found in 7.7-58.7% of patients in studies.[14,19] Some metabolic changes together with anemia are thought to be involved in its pathogenesis.15 Although half and half nail is not a specific finding in CKD, it is observed in approximately 40% of patients on HD and it is thought to develop due to increased melanocyte-stimulating hormone.[9] It has also been reported that this nail sign disappears after renal transplantation.[3] Its frequency has been reported to be 15.7-51% in different studies.[4,7,9,10,14,19] In our study, in patients with subungual hyperkeratosis this finding was compatible with fungal infection.

Mucosal findings are also frequently observed in patients on maintenance hemodialysis. In our study, mucosal pallor and dry mouth were observed most frequently. While mucosal findings were associated with anemia in one study, this relationship was not shown in our study.[11] Differently, patients with mucosal findings consisted of older patients. In a study examining oral mucosal findings, mucosal findings were found with a rate of 48%; the most common findings were dry mouth, taste disturbance and burning mouth.[20] Malnutrition, anemia, impaired salivary gland function and sensitivity to oral pathogens may play a role in the formation of these findings.[20] This situation also leads to candida infection and the development of black hairy tongue. In our study, black hairy tongue and candida stomatitis were found in patients. The frequency of candida in saliva was also found to be higher in patients on HD.[21] While macroglossia has been reported at different rates in patients with CKD, this finding was not observed in any patient in our study.[9]

Hair findings were observed only in female patients and this difference was statistically significant. Lusterless hair was the most common hair finding in maintenance hemodialysis patients. Lusterless hair is a finding frequently shown in other studies.[9-11] This finding has been tried to be explained with anemia, decreased sebum secretion and elevated parathyroid hormone.[11] In our study, there was no laboratory finding associated with lusterless hair.

The most common infections were onychomycosis (14%) and oral candida infection (14%). One patient (2.3%) had scabies. It is thought that impairment in the cellular immune system and a decrease in the number of T lymphocytes in patients with CKD facilitate the development of infection.[9]

In our study, calcinosis cutis, one of the specific dermatoses, was found in only one patient. The patient's gender was female, the lesions were located near the knee, elbow and hip joints and parathyroid hormone and calcium levels were markedly elevated. Calcinosis cutis is a benign nodular calcification caused by the accumulation of insoluble calcium deposits in the skin and subcutaneous tissue. It appears as hard papules, nodules and plaques and can be excreted through the epidermis. It is most commonly seen in periarticular areas and fingertips. Its severity is related to calcium and phosphorus levels.[6] Although other specific dermatoses including calciphylaxis, acquired perforating dermatoses, bullous disease and nephrogenic systemic fibrosis have been reported in studies, they were not found in our study.

Study Limitations

The study's sample size is relatively small, which may limit the generalizability of the findings to a larger population. The study is conducted at a single center, which may limit the diversity of patient demographics and experiences,

potentially leading to selection bias. The study lacks a control group, which would be essential for comparing the observed findings with a group of individuals not undergoing HD. The study identifies associations between certain variables and findings but does not establish causative relationships, making it difficult to draw definitive conclusions about the etiology of these findings.

CONCLUSION

Various skin, nail, hair and mucous membrane findings are observed in patients with CKD due to both renal disease and HD. At least one of these findings can be seen in patients and negatively affect quality of life. Regular follow-up of the patients is important for the detection, prevention and treatment of these findings.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Medicana International Ankara Hospital Ethics Committee (Date: 14.07.2023, Decision No: 16).

Informed Consent: Written informed consent form was obtained from the patients.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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